Microwave-Assisted Synthesis of Acetophenone (per-*O*-acetylated- β -*D*-glucopyranosyl)- thiosemicarbazones

NGUYEN DINH THANH*, NGUYEN THI KIM GIANG and LE THE HOAI

Faculty of Chemistry,
College of Science, Hanoi National University,
19 Le Thanh Tong, Ha Noi 10000, Viet nam.

nguyendinhthanh@hus.edu.vn

Received 3 November 2009; Accepted 2 January 2010

Abstract—Thirteen new substituted acetophenone (2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazones (**3**) were synthesized by reaction of 2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl thiosemicarbazide (**1**) and substituted acetophenones (**2**). The reaction was performed using microwave-assisted method. The compounds (**3**) have remarkable antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus epidermidis* and *Candida albicans*.

Keywords: Glucopyranosyl thiosemicarbazide, Thiosemicarbazones, Microwave-assisted method, Acetophenone.

Introduction

Thiosemicarbazones are a class of small molecules that have been evaluated over the last 50 years as antivirals and as anticancer therapeutics, as well as for their parasitocidal action against *Plasmodium falciparum* and *Trypanosoma cruzi* which are the causative agents of malaria and Chagas's disease, respectively¹. The chemistry of thiosemicarbazide derivatives of saccharides is interested²⁻⁴. These compounds arouse interest as versatile intermediates for preparing various (*e.g.*, heterocyclic) derivatives as well. Thiosemicarbazones can be used for making electrodes⁵, or complexes formation of metallic ions⁶. Thiosemicarbazones exhibit various biological activities such as antituberculosis⁷, antimicrobial⁸, anti-inflammatory⁹, antiviral, anticonvulsant¹⁰, antihypertensive¹¹, local anesthetic¹², anticancer¹³, hypoglycemic¹⁴ and cytotoxic activities, among others¹⁵.

A number of glucosyl thiosemicarbazide derivatives showed significant *in vivo* anti-microorganisms and *in vitro* antioxidant activity, which could be used as leads for the development of effective anti-atherosclerotic agents¹⁶. On the other hand, these molecules can also serve as phosphane-free multidentate ligands for transition-metal catalysis and they are efficient ligands for palladium-catalyzed coupling reactions in air¹⁷. In the past, some papers have been published for the synthesis of aldehyde/ketone 4-(per-*O*-acetylated- β -*D*-glucopyranosyl)-thiosemicarbazones and their corresponding deacetylated analogues¹⁸. The main synthetic step for the synthesis of these molecules is being the reaction of a glucosyl thiosemicarbazide with a carbonyl compound.

Continuing our studies on the synthesis and the reactivity of peracetylated glucopyranosyl isothiocyanates and thiosemicarbazides¹⁹, we report here a systematic study for the synthesis and spectral characterization of a series of aromatic ketone 4-(β -*D*-glucopyranosyl)-thiosemicarbazones using microwave-assisted method²⁰.

Experimental

All the starting materials and reagents were purchased from commercial suppliers and used after further purification. 2,3,4,6-Tetra-*O*-acetyl- β -*D*-glucopyranosyl isothiocyanate was prepared by the reaction of per-*O*-acetylated- β -*D*-glucopyranosyl bromide (prepared from *D*-glucose)^{21a} with lead thiocyanate in dried toluene^{21b} and 2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl thiosemicarbazide were synthesized by known method^{18b,22}.

Physical measurements

Melting points were determined by open capillary method on STUART SMP3 instrument (BIBBY STERILIN-UK) and are uncorrected. IR spectra (KBr disc) were recorded on an Impact 410 FT-IR Spectrometer (Nicolet, USA). ¹H and ¹³C NMR spectra were recorded on Bruker Avance Spectrometer AV500 (Bruker, Germany) at 500.13 MHz and 125.77 MHz, respectively, using DMSO-*d*₆ as solvent and TMS as an internal standard. The chemical shifts are expressed in δ ppm scale down field from TMS and proton signals are indicated as s = singlet, d = doublet, t = triplet and m = multiplet. HRMS spectra were recorded on mass spectrometer AutoSpec Premier (WATERS, USA) using EI 70 eV.

General procedure for synthesis of substituted acetophenone 2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl thiosemicarbazones (**3a-m**)

A suspension mixture of (2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)thiosemicarbazide **1** (1 mmol) and corresponding substituted acetophenone **2** (1 mmol) and glacial acetic acid (0.05 mL) in absolute methanol (5 mL) was irradiated with reflux for 5-7 minutes in microwave oven. The suspension mixture became clear solution after irradiating in 3-4 minutes. After reaction the mixture was cooled to room temperature, the colorless crystals were filtered with suction. The crude product was recrystallized from ethanol or ethanol/toluene to yield corresponding acetophenone (2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazones **3**.

4-Nitroacetophenone(2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazone (**3a**)

White solid, mp 217-218 °C; yield 77%; $[\alpha]_D^{25}$ -58.0 (*c* 1.0, CHCl₃); IR (KBr, cm⁻¹): 3354, 3318, 1744, 1229.0, 1034, 1370, 1582; ¹H NMR (DMSO-*d*₆): δ 11.01 (s, 1H, H-2''), 8.81 (d, 1H, *J*=9.0 Hz, H-4''), 8.22 (m, 4H, H-2' & H-6', H-3' & H-5'), 5.95 (t, 1H, *J*=9.25 Hz, H-1), 5.45 (t, 1H, *J*=9.5 Hz, H-3), 5.35 (t, 1H, *J*=9.25 Hz, H-2), 4.98 (t, 1H, *J*=9.5 Hz, H-4), 4.22 (dd, *J*=12.25, 4.75 Hz, 1H, H-6a), 4.10 (ddd, *J*=9.95, 4.75, 2.25 Hz, 1H, H-5), 3.99

(dd, $J=12.25, 2.5$ Hz, 1H, H-6b), 2.39 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.99-2.01 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.7 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 147.6 (C=N), 147.1 (C-4'), 143.5 (C-1'), 127.9 (C-3' & C-5'), 123.2 (C-2' & C-6'), 81.4 (C-1), 70.8 (C-2), 72.5 (C-3), 72.2 (C-5), 68.0 (C-4), 61.7 (C-6), 20.2-20.4 ($4\times\text{CH}_3\text{CO}$), 14.3 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 568.1432 (M^+), calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_{11}\text{S}$ =568.1475 Da.

3-Nitroacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone (3b)

White solid, mp 196-197 °C, lit.^{18c} mp 184-186 °C; yield 78%; $[\alpha]_D^{25}$ -78.0 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3325, 3246, 1749.0, 1372, 1617, 1226, 1045; ^1H NMR (DMSO- d_6): δ 10.98 (s, 1H, H-2''), 8.77 (d, 1H, $J=9.0$ Hz, H-4''), 8.56 (s, 1H, H-2'), 8.44 (d, $J=8.0$ Hz, 1H, H-4'), 8.27 (t, $J=7.5$ Hz, 1H, H-6'), 7.71 (t, $J=8.0$ Hz, 1H, H-5'), 5.94 (t, 1H, $J=9.0$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.29 (t, 1H, $J=9.0$ Hz, H-2), 4.98 (t, 1H, $J=9.5$ Hz, H-4), 4.22 (dd, $J=12.5, 5$ Hz, 1H, H-6a), 4.09 (ddd, $J=7, 3.75, 2$ Hz, 1H, H-5), 4.00 (dd, $J=11.25, 1.5$ Hz, 1H, H-6b), 2.41 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.95-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.6 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 148.1 (C-3'), 147.6 (C=N), 139.1 (C-1'), 133.0 (C-2'), 129.7 (C-4'), 123.9 (C-6'), 121.3 (C-5'), 81.4 (C-1), 72.4 (C-3), 72.2 (C-5), 70.8 (C-2), 68.0 (C-4), 61.7 (C-6), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 14.5 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 568.1316 (M^+), calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_{11}\text{S}$ =568.1475 Da.

4-Chloroacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone(3c)

White solid, mp 199-201 °C; yield 85%; $[\alpha]_D^{25}$ -86.5 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3323, 3298, 1749.0, 1614, 1370, 1225, 1098; ^1H NMR (DMSO- d_6): δ 10.83 (s, 1H, H-2''), 8.67 (d, 1H, $J=9.25$ Hz, H-4''), 7.97 (t, 2H, $J=8.6$ Hz, H-2' & H-6'), 7.47 (d, 2H, $J=8.6$ Hz, H-2' & H-6'), 5.93 (t, 1H, $J=9.0$ Hz, $J_{1,2}=9.25$ Hz, H-1), 5.43 (t, 1H, $J=9.5$ Hz, H-3), 5.31 (t, 1H, $J=9.25$ Hz, $J=9.5$ Hz, H-2), 4.97 (t, 1H, $J=9.75$ Hz, H-4), 4.21 (dd, $J=12.25, 4.75$ Hz, 1H, H-6a), 4.07 (ddd, $J=10, 4.75, 2.25$ Hz, 1H, H-5), 3.99 (dd, $J=12.25, 2.25$ Hz, 1H, H-6b), 2.32 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.94-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.4 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 148.5 (C=N), 136.1 (C-4'), 134.3 (C-1'), 128.6 (C-3' & C-5'), 128.2 (C-2' & C-6'), 81.3 (C-1), 72.5 (C-3), 72.1 (C-5), 70.8 (C-2), 68.0 (C-4), 61.7 (C-6), 20.2-20.5 ($4\times\text{CH}_3\text{CO}$), 14.3 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 557.1230/559.1209 (M^+), calcd. for $\text{C}_{23}\text{H}_{28}\text{ClN}_3\text{O}_9\text{S}$ =557.1235/559.1205 Da.

4-Bromoacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)thiosemicarbazone(3d)

White solid, mp 205-206 °C, lit.^{18c} mp 186-88 °C; yield 90%; $[\alpha]_D^{25}$ -98.7 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3354, 3318, 1749.0, 1602, 1373, 1230, 1041; ^1H NMR (DMSO- d_6): δ 10.84 (s, 1H, H-2''), 8.67 (d, 1H, $J=9.0$ Hz, H-4''), 7.88 (d, 2H, $J=8.3$ Hz, H-2' & H-6'), 7.59 (d, 2H, $J=8.3$ Hz, H-2' & H-6'), 5.94 (t, 1H, $J=9.0$ Hz, $J_{1,2}=9.0$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.32 (t, 1H, $J=9.0$ Hz, $J=9.1$ Hz, H-2), 4.98 (t, 1H, $J=9.5$ Hz, H-4), 4.22 (dd, $J=12.25, 4.75$ Hz, 1H, H-6a), 4.08 (ddd, $J=10, 5.75, 2$ Hz, 1H, H-5), 3.99 (d, $J=11.5$ Hz, 1H, H-6b), 2.32 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.95-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.4 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 148.5 (C=N), 136.5 (C-4'), 131.1 (C-3' & C-5'), 128.8 (C-2' & C-6'), 123.1 (C-1'), 81.3 (C-1), 72.5 (C-3), 72.2 (C-5), 70.8 (C-2), 68.0 (C-4), 61.7 (C-6), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 14.2 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 601.0568/603.0494 (M^+), calcd. for $\text{C}_{23}\text{H}_{28}\text{BrN}_3\text{O}_9\text{S}$ =601.0729/ 603.0709 Da.

Acetophenone (2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone(3e)

White solid, mp 208-209 °C; yield 77%; $[\alpha]_D^{25}$ -45.5 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3354, 3318, 1743, 1620, 1371, 1234, 1039; ^1H NMR (DMSO- d_6): δ 10.81 (s, 1H, H-2''), 8.63 (d, 1H, $J=9.5$ Hz, H-4''), 7.93 (m, 2H, H-2' & H-6'), 7.42 (m, 3H, H-3', H-4' & H-5'), 5.94

(t, 1H, $J=9.5$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.31 (t, 1H, $J=9.5$ Hz, H-2), 4.98 (t, 1H, $J=9.87$ Hz, H-4), 4.21 (dd, $J=12.0$, 5.0 Hz, 1H, H-6a), 4.07 (ddd, $J_{5,4}=9.87$, 4.75, 2.25 Hz, 1H, H-5), 4.00 (dd, $J=11.25$, 2.5 Hz, 1H, H-6b), 2.34 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.99–2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.3 (C=S), 169.1–169.9 ($4\times\text{C}=\text{O}$), 149.7 (C=N), 137.6 (C-1'), 129.5 (C-4'), 128.2 (C-2' & C-6'), 126.7 (C-3' & C-5'), 81.3 (C-1), 72.4 (C-3), 72.1 (C-5), 70.7 (C-2), 68.1 (C-4), 61.8 (C-6), 20.2–20.5 ($4\times\text{CH}_3\text{CO}$), 14.4 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 523.1556 (M^+), calcd. for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_9\text{S}=523.1624$ Da.

4-Methylacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)thiosemicarbazone(3f)

White solid, mp 200–201 °C; yield 83%; $[\alpha]_{\text{D}}^{25} -66.4$ (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3356, 3305, 1748, 1600, 1378, 1225, 1039; ^1H NMR (DMSO- d_6): δ 10.76 (s, 1H, H-2''), 8.59 (d, 1H, $J=9.3$ Hz, H-4''), 7.82 (d, 2H, $J=8.2$ Hz, H-2' & H-6'), 7.23 (d, 2H, $J=8.1$ Hz, H-2' & H-6'), 5.93 (t, 1H, $J=9.3$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.30 (t, 1H, $J=9.3$ Hz, H-2), 4.98 (t, 1H, $J=9.5$ Hz, H-4), 4.21 (dd, $J=12.5$, 5 Hz, 1H, H-6a), 4.19 (dd, $J=12.25$, 2.25 Hz, 1H, H-6b), 4.06 (ddd, $J_{5,4}=10.0$, 4.75, 2.25 Hz, 1H, H-5), 2.32 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 2.31 (s, 3H, ArCH_3), 1.99–2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.2 (C=S), 169.3–169.9 ($4\times\text{C}=\text{O}$), 149.8 (C=N), 139.3 (C-1'), 134.5 (C-4'), 128.8 (C-2' & C-6'), 126.7 (C-3' & C-5'), 81.2 (C-1), 72.5 (C-3), 72.1 (C-5), 70.7 (C-2), 68.1 (C-4), 61.8 (C-6), 20.8 (ArCH_3), 20.2–20.8 ($4\times\text{CH}_3\text{CO}$), 14.3 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 537.1770 (M^+), calcd. for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_9\text{S}=537.1781$ Da.

4-Methoxyacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)thiosemicarbazone (3g)

White solid, mp 190–191 °C, lit.^{18f} mp 192–198 °C; yield 78%; $[\alpha]_{\text{D}}^{25} -48.0$ (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3390, 3332, 1745, 1608, 1378, 1223, 1038; ^1H NMR (DMSO- d_6): δ 10.73 (s, 1H, H-2''), 8.58 (d, 1H, $J=9.0$ Hz, H-4''), 7.89 (d, 2H, $J=8.9.0$ Hz, H-2' & H-6'), 6.95 (d, 2H, $J=8.9.0$ Hz, H-3' & H-5'), 5.93 (t, 1H, $J=9.5$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.30 (t, 1H, $J=9.5$ Hz, H-2), 4.98 (t, 1H, $J=9.5$ Hz, H-4), 4.21 (dd, $J=12.5$, 5.0 Hz, 1H, H-6a), 4.06 (ddd, $J=10.0$, 4.75, 2.0 Hz, 1H, H-5), 3.99 (dd, $J=12.5$, 2.0 Hz, 1H, H-6b), 3.81(s, 3H, OCH_3), 2.30 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.99–2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.0 (C=S), 169.3–169.9 ($4\times\text{C}=\text{O}$), 160.5 (C_4'), 149.7 (C=N), 129.6 (C_1'), 128.4 (C_2' & C_6'), 113.6 (C_3' & C_5'), 81.2 (C_1), 72.5 (C_3), 72.1 (C_5), 70.8 (C_2), 68.1 (C_4), 61.8 (C_6), 55.2 (OCH_3), 20.3–20.5 ($4\times\text{CH}_3\text{CO}$), 14.2 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 553.1712 (M^+), calcd. for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_{10}\text{S}=553.1730$ Da.

4-Ethoxyacetophenone (2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone (3h)

White solid, mp 184–185 °C; yield 86%; $[\alpha]_{\text{D}}^{25} -79.2$ (c 1.0, CHCl_3); IR (KBr): 3375, 3318, 1748, 1604, 1374, 1227, 1039; ^1H NMR (DMSO- d_6): δ 10.71 (s, 1H, H-2''), 8.58 (d, 1H, $J=9.5$ Hz, H-4''), 7.87 (d, 2H, $J=8.9.0$ Hz, H-2' & H-6'), 6.94 (d, 2H, $J=8.9.0$ Hz, H-2' & H-6'), 5.94 (t, 1H, $J=9.5$ Hz, $J_{1,2}=9.2$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.31 (t, 1H, $J=9.3$ Hz, $J=9.5$ Hz, H-2), 4.99 (t, 1H, $J=9.5$ Hz, $J=9.75$ Hz, H-4), 4.21 (dd, $J=12.5$, 5.0 Hz, 1H, H-6a), 4.07 (ddd, $J_{5,4}=10.25$ Hz, $J=6.5$ Hz, $J=2.5$ Hz, 1H, H-5), 4.05 (q, 2H, $J=7.0$ Hz, OCH_2), 3.40 (dd, $J=12.25$, 2.25 Hz, 1H, H-6b), 1.34 (t, 3H, $J=7.0$ Hz, OCH_2CH_3), 2.30 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.99–2.01 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.0 (C=S), 169.9–169.3 ($4\times\text{C}=\text{O}$), 159.8 (C-4'), 149.7 (C=N), 129.5 (C-1'), 128.3 (C-3' & C-5'), 114.0 (C-2' & C-6'), 81.3 (C-1), 72.5 (C-3), 72.2 (C-5), 70.8 (C-2), 68.1 (C-4), 63.2 (OCH_2CH_3), 61.8 (C-6), 20.5–20.2 ($4\times\text{CH}_3\text{CO}$), 14.5 ($\text{CH}_3\text{C}=\text{N}$), 14.2 (OCH_2CH_3); HRMS: 567.1885 (M^+), calcd. for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_{10}\text{S}=567.1887$ Da.

3-Nitro-4-methylacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone (3i)

White solid, mp 223–224 °C; yield 81%; $[\alpha]_{\text{D}}^{25} -67.3$ (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3325, 3246,

1621, 1748, 1370, 1222, 1046; ^1H NMR (DMSO- d_6): δ 10.92 (s, 1H, H-2''), 8.73 (d, 1H, $J=9.1$ Hz, H-4''), 8.35 (d, $J=1.5$ Hz, 1H, H-2'), 8.20 (d, $J=8.0$ Hz, 1H, H-5'), 7.54 (d, $J=8.0$ Hz, 1H, H-6'), 5.92 (t, 1H, $J=9.2$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.28 (t, 1H, $J=9.25$ Hz, H-2), 4.98 (t, 1H, $J=9.5$ Hz, H-4), 4.22 (dd, $J=12.25$, 4.75 Hz, 1H, H-6a), 4.08 (ddd, $J=9.0$, 3.5, 2.25 Hz, 1H, H-5), 4.01 (dd, $J=11.5$, 2.0 Hz, 1H, H-6b), 2.65 (s, 3H, ArCH_3), 2.52 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.95-2.01 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.5 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 149.5 (C-3'), 147.5 (C=N), 136.6 (C-1'), 133.2 (C-2'), 132.5 (C-6'), 130.8 (C-4'), 121.9 (C-5'), 81.4 (C-1), 70.7 (C-2), 72.4 (C-3), 72.2 (C-5), 68.1 (C-4), 61.7 (C-6), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 18.8 (ArCH_3), 14.3 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 582.1663 (M^+), calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_{11}\text{S}$ =582.1632 Da.

3-Nitro-4-methoxyacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone (3j)

White solid, mp 222-223 °C; yield 77%; $[\alpha]_D^{25}$ -78.6 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3340, 1747, 1617, 1379, 1226, 1037; ^1H -NMR (DMSO- d_6): δ 10.85 (s, 1H, H-2''), 8.71 (d, 1H, $J=9.0$ Hz, H-4''), 8.33 (d, $J=2.5$ Hz, 1H, H-2'), 8.21 (dd, $J=8.75$, 2.25 Hz, 1H, H-6'), 7.37 (d, $J=9.0$ Hz, 1H, H-5'), 5.90 (t, 1H, $J=9.0$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.27 (t, 1H, $J=9.25$, H-2), 4.97 (t, 1H, $J=9.75$ Hz, H-4), 4.22 (dd, $J=12.25$, 4.75 Hz, 1H, H-6a), 4.06 (ddd, 1H, $J=10.0$ Hz, 4.75 Hz, 2.25 Hz, H-5), 3.99 (d, 1H, $J=11.0$ Hz, 2.0 Hz, 1H, H-6b), 3.97 (s, 3H, OCH_3), 2.33 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.98-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.4 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 152.3 (C-4'), 147.6 (C=N), 139.7 (C-1'), 132.2 (C-3'), 122.7 (C-2'), 129.8 (C-5'), 113.8 (C-6'), 81.4 (C-1), 72.4 (C-3), 72.2 (C-5), 70.7 (C-2), 68.1 (C-4), 61.7 (C-6), 56.9 (OCH_3), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 14.2 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 598.1598 (M^+), calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_{12}\text{S}$ =598.1581 Da.

3-Nitro-4-ethoxyacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone (3k)

White solid, mp 203-204 °C; yield 78%; $[\alpha]_D^{25}$ -98.0 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3340, 3203, 1750, 1622, 1373, 1238, 1042; ^1H NMR (DMSO- d_6): δ 10.85 (s, 1H, H-2''), 8.70 (d, 1H, $J=9.5$ Hz, H-4''), 8.32 (d, 1H, H-5'), 8.19 (m, 1H, H-2'), 7.37 (s, 1H, H-6'), 5.91 (t, 1H, $J=9.25$ Hz, H-1), 5.44 (t, 1H, $J=9.5$ Hz, H-3), 5.27 (t, 1H, $J=9.5$ Hz, H-2), 4.97 (t, 1H, $J=9.5$ Hz, H-4), 4.28 (q, 2H, $J=7.0$ Hz, OCH_2CH_3), 4.22 (dd, $J=12.5$, 5.0 Hz, 1H, H-6a), 4.07 (ddd, $J=10.0$, 4.75, 2.25 Hz, 1H, H-5), 3.98 (dd, $J=12.25$, 2.25 Hz, 1H, H-6b), 2.49 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.95-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$), 1.35 (t, 3H, $J=7.0$ Hz, OCH_2CH_3); ^{13}C NMR (DMSO- d_6): δ 179.5 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 151.4 (C-4'), 149.7 (C-3'), 147.6 (C=N), 139.9 (C-1'), 128.4 (C-5'), 122.6 (C-2'), 114.6 (C-6'), 81.4 (C-1), 72.4 (C-3), 68.1 (C-4), 72.2 (C-5), 70.7 (C-2), 61.7 (C-6), 65.3 (OCH_2CH_3), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 14.3 ($\text{CH}_3\text{C}=\text{N}$), 14.2 (OCH_2CH_3); HRMS: 612.1737 (M^+), calcd. for $\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_{12}\text{S}$ =612.1741 Da.

3-Nitro-4-chloroacetophenone(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-thiosemicarbazone (3l)

White solid, mp 215-216 °C; yield 83%; $[\alpha]_D^{25}$ -88.8 (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3332, 3239, 1747, 1611, 1370, 1223, 1043; ^1H NMR (DMSO- d_6): δ (ppm) 10.97 (s, 1H, H-2''), 8.81 (d, 1H, $J=9.0$ Hz, H-4''), 8.50 (d, $J=2.0$ Hz, 1H, H-2'), 8.22 (dd, $J=8.75$, 2.25 Hz, 1H, H-6'), 7.79 (d, 1H, $J=9.0$ Hz, H-5'), 5.90 (t, 1H, $J=9.0$ Hz, H-1), 5.43 (t, 1H, $J=9.5$ Hz, H-3), 5.28 (t, 1H, $J=9.5$ Hz, H-2), 4.97 (t, 1H, $J=9.5$ Hz, H-4), 4.22 (dd, $J=12.25$, 4.75 Hz, 1H, H-6a), 4.07 (ddd, $J=6.25$, 5.0, 2.5 Hz, 1H, H-5), 3.99 (dd, 1H, $J=11.5$, 2.0 Hz, H-6b), 2.35 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.93-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); ^{13}C NMR (DMSO- d_6): δ 179.7 (C=S), 169.3-169.9 ($4\times\text{C}=\text{O}$), 148.2 (C-4'), 146.5 (C=N), 138.4 (C-3'), 131.4

(C-1'), 131.2 (C-5'), 125.1 (C-2'), 122.9 (C-6'), 81.5 (C-1), 72.5 (C-3), 72.3 (C-5), 70.7 (C-2), 68.1 (C-4), 61.7 (C-6), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 14.193 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 602.1076/604.1046 [$\text{M}^+/(M+2)^+$], calcd. for $\text{C}_{24}\text{H}_{27}^{35}\text{ClN}_4\text{O}_{11}\text{S}/\text{C}_{24}\text{H}_{27}^{37}\text{ClN}_4\text{O}_{11}\text{S}=602.1086/604.1056$ Da.

3-Nitro-4-bromoacetophenone(2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazone (3m)

White solid, mp 204-205 °C; yield 85%; $[\alpha]_D^{25} -89.0$ (c 1.0, CHCl_3); IR (KBr, cm^{-1}): 3327, 1750, 1620, 1374, 1226, 1035; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 10.96 (s, 1H, H-2''), 8.80 (d, 1H, $J=9.0$ Hz, H-4''), 8.46 (d, $J=2$ Hz, 1H, H-2), 8.11 (dd, $J=8.5$, 2.0 Hz, 1H, H-6'), 7.91 (d, $J=8.5$ Hz, 1H, H-5), 5.90 (t, 1H, $J=9.0$ Hz, H-1), 5.43 (t, 1H, $J=9.5$ Hz, H-3), 5.28 (t, 1H, $J=9.5$ Hz, H-2), 4.97 (t, 1H, $J=9.5$ Hz, H-4), 4.07 (ddd, $J=10.0$, 4.75, 2.25 Hz, 1H, H-5), 4.22 (dd, $J=12.5$, 4.5 Hz, 1H, H-6a), 3.98 (dd, $J=12.5$, 2.0 Hz, 1H, H-6b), 2.35 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 1.93-2.00 (s, 12H, $4\times\text{CH}_3\text{CO}$); $^{13}\text{C NMR}$ ($\text{DMSO}-d_6$): δ 179.7 (C=S), 169.4-170.0 ($4\times\text{C}=\text{O}$), 150.3 (C-4'), 146.6 (C=N), 138.4 (C-3'), 134.3 (C-1'), 131.3 (C-5'), 122.8 (C-2'), 113.3 (C-6'), 81.5 (C-1), 72.3 (C-5), 72.5 (C-3), 70.7 (C-2), 68.1 (C-4), 61.7 (C-6), 20.3-20.5 ($4\times\text{CH}_3\text{CO}$), 14.2 ($\text{CH}_3\text{C}=\text{N}$); HRMS: 646.0589/648.0557 [$\text{M}^+/(M+2)^+$], calcd. for $\text{C}_{24}\text{H}_{27}^{79}\text{BrN}_4\text{O}_{11}\text{S}/\text{C}_{24}\text{H}_{27}^{81}\text{BrN}_4\text{O}_{11}\text{S}=646.0580/648.0560$ Da.

Results and Discussion

The synthesis of the title compound is outlined in Scheme 1. Condensation of 4-(tetra-*O*-acetyl- β -*D*-glucopyranosyl)thiosemicarbazide (**1**)^{1c, 6-8} with a number of acetophenones afforded acetophenone 4-(tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazones (**3**). This syntheses was carried out using minimum amount of solvent (methanol) comparing conventional heating methods (3-5 mL volume vs. 20-30 mL, respectively). Reaction time was from 40 to 50 minutes depending substituent's nature: withdrawing substituents need shorter reaction time than donating ones (Table 1). In the first period of reaction when reaction was starting to irradiate about 10-15 minute, the pasty mixture of reagents in methanol was dissolved and the reaction became homogenous. In the final period of reaction, the solid product appeared and precipitated out. The solid thiosemicarbazones (**3**) were filtered by suction and recrystallized from ethanol or ethanol/toluene (1:1 in volume)^{11,12}. These compounds can be dissolved in ethanol, toluene, chloroform, DMF and had high melting points. Compounds **3b**, **3d** and **3g** have been already reported in references¹⁸, so other remaining acetophenone 4-(tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazones (**3**) have been synthesized for the first time. All the products were characterized by IR, $^1\text{H NMR}$ and $^{13}\text{C NMR}$, and mass spectra.

Scheme 1.

The IR spectra of compounds **3** showed characteristic absorptions in the range of 3323–3390 cm^{-1} and 3298–3332 cm^{-1} (N–H bond), 1743–1749, 1223–1234 cm^{-1} and 1038–1098 cm^{-1} (ester), 1370–1378 cm^{-1} (C=S), and 1620–1600 cm^{-1} (C=N bond). In the ^1H NMR spectra of **3**, the aromatic proton H-1 is represented as a triplet at the range 5.90–5.95 ppm due to the coupling with the N(4'')–H and the H-2. The coupling constant $J_{\text{H-1,H-2}}$ (9.0–9.5 Hz) is an evidence which confirms the β configuration in compounds **3**^{12–18}. The NH proton of the thioamide functionality of compounds **3** appeared at 10.71–10.98 ppm (singlet) for N(2'')H and 8.77–8.58 ppm (doublet, $J_{\text{NH,H-1}}=9.0\text{--}9.5$ Hz) for N(4'')H. The ^{13}C -NMR spectra showed the thiocarbonyl carbon atom with chemical shift at $\delta=179.0\text{--}179.7$ ppm¹⁸.

Table 1. Substituted acetophenone (2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)thiosemicarbazones (**3a-m**).

Entry	R	Microwave Irradiation Time,min	Entry	R	Microwave Irradiation Time, min
3a	4-NO ₂	6	3h	4-OC ₂ H ₅	8
3b	3-NO ₂	6	3i	3-NO ₂ -4-Me	7
3c	4-Cl	6	3j	3- NO ₂ -4-OMe	7
3d	4-Br	6	3k	3- NO ₂ -4-OEt	7
3e	H	8	3l	3- NO ₂ -4-Cl	7
3f	4-CH ₃	8	3m	3- NO ₂ -4-Br	7
3g	4-OCH ₃	8			

^{a)} lit.^{18e}: mp 184–186 °C; ^{b)} lit.^{18e}: mp 186–88 °C; ^{c)} lit.^{18f}: mp 192–198 °C.

It has previously been found that thiosemicarbazone derivatives relating to the stereochemistry of the C=N bond, can exist in the *E* or *Z* form or as a mixture of *E/Z* isomers, usually with the *E* form being the major isomer²³. *E/Z*-Isomeric ratios is depended on the substituents' nature and its position on the thiosemicarbazone moiety and the solvent. The correct configuration then can be determined by ^1H NMR spectroscopy, as the N(4'')H on NH–N=C group appears at $\delta=9\text{--}12$ ppm for the *E* form, and $\delta=14\text{--}15$ ppm for the *Z* form²³. Thiosemicarbazones **3** had remarkable anti-microorganism activities (Table 2). In amount of compounds **3** was 20 $\mu\text{g/mL}$, the biological activities were insignificant for *E. coli*, *S. epidermidis* and *C. albicans*. In higher amount (40 $\mu\text{g/mL}$ and 60 $\mu\text{g/mL}$) most these compounds had significant biological activities for those microorganisms.

Table 2. Exploration of biological activities of thiosemicarbazones **3a-m**.

Entry	R	Diameter of antibacterial ring, mm					
		<i>E. coli</i>		<i>S. epidermidis</i>		<i>C. albicans</i>	
		40 $\mu\text{g/mL}$	60 $\mu\text{g/mL}$	40 $\mu\text{g/mL}$	60 $\mu\text{g/mL}$	40 $\mu\text{g/mL}$	60 $\mu\text{g/mL}$
3a	4-NO ₂	20	20	24	28	20	25
3b	3-NO ₂	20	20	23	26	20	25
3c	4-Cl	20	20	25	30	18	23
3d	4-Br	15	18	20	25	18	24
3e	H	20	20	23	26	20	25
3f	4-CH ₃	20	20	23	25	20	25
3g	4-OCH ₃	20	20	23	26	20	25
3h	4-OC ₂ H ₅	20	20	20	26	20	25
3i	3-NO ₂ -4-Me	20	20	20	25	20	25
3j	3- NO ₂ -4-OMe	20	20	24	27	18	23
3k	3- NO ₂ -4-OEt	20	20	25	30	20	25
3l	3- NO ₂ -4-Cl	20	20	20	26	20	26
3m	3- NO ₂ -4-Br	20	20	24	28	21	26

Conclusion

We have developed a highly efficient method for the synthesis of (2,3,4,6-tetra-*O*-acetyl- β -*D*-glucopyranosyl)-thiosemicarbazones of acetophenones under microwave-assisted heating conditions.

Acknowledgments

Financial support for this work was provided by Scientific Research Fund-Hanoi National University (Grant QGTD.08.03).

References

- Greenbaum D C, Mackey Z, Hansell E, Doyle P, Gut J, Caffrey C R, Lehrman J, Rosenthal P J, McKerrow J H and Chibale K, *J Med Chem.*, 2004, **47**, 3212.
- Bo Yang, Shu-sheng Zhang and Hui-xiang Li, *Chem Res Chin Univ.*, 2006, **22** 738.
- Alho M A M and D'Accorso N B, *Carbohydr Res.*, 2000, **328**, 481.
- Zhang S -S, Ye S -J, Li X -M, Gu S -S and Liu Q, *Chem Res Chin Univ.*, 2000, **21**, 545.
- Ganlali M R, Hosseini M, Salavati-Niasari M, Poursaberi T, Shamsipur M, Javanbakht M and Hashemi O R, *Electroanalysis*, 2002, **14**, 7.
- Sarma L S, Kumar J R, Reddy K J and Reddy A V J, *Agric Food Chem.*, 2005, **53**, 5492.
- Desai N C, Shucla H K, Parekh B R and Thaker K A J, *Indian Chem Soc.*, 1984, **61**, 455.
- Mamolo M G, Vio L and Banfi E, *IL Farmaco*, 1996, **51**, 71.
- Abanauskas L, Kalcas V, Udrenaitė E, Gaidelis P, Brukstus A and Dauksas A, *Pharmazie*, 2001, **56**, 617.
- Chapleo C B, Myers P L, Smith A C, Stilling M R, Tulloch I F and Walter D S, *J Med Chem.*, 1988, **31**, 7.
- Turner S, Myers M, Gadie B, Hale S A, Horsley A, Nelson A J, Pape R, Saville J F, Doney J C and Berridge T L, *J Med Chem.*, 1988, **31**, 907.
- Mazzone G, Pignatello R, Mazzone S, Panico A, Penisi G, Castana R and Mazzone P, *IL Farmaco*, 1993, **48** 1207
- Chou J Y, Lai S H, Pan S L, Jow G M, Chern J W and Guh J H, *Biochem Pharmacol.*, 2003, **66**, 115
- Hana M A, Girges M M, Rasala D and Gawinecki R, *Arzneim-Forsch / Drug Res.*, 1995, **45**, 1074.
- Holla B S, Malini K V, Rao B S, Sarojini B K, Kumari N S, *Eur J Med Chem.*, 2003, **38**, 313.
- Kovala-Demertzi D, Yadav P N, Wiecek J, Skoulika S, Varadinova T and Demertzi M A, *J Inorg Biochem.*, 2006, **100**, 1558.
- Kostas I D, Heropoulos G A, Kovala-Demertzi D, Yadav P N, Jasinski J P, Demertzi M A, Andreadaki F J, Vo-Thanh G, Petit A and Loupy A, *Tetrahedron Lett.*, 2006, **47**, 4403.
- (a) Bognár R, Somogyi L, Szilágyi L and Györgydeák Z, *Carbohydr Res.*, 1967, **5**, 320; (b) Tashpulatov A A, Rakhmatullaev V A and Ismailov N, *Zh Org Khim.*, 1988, **24**, 1893; (c) Cao K, Wang Z and Zhao X, *Jingxi Shiyong Huagong*, 2003, 42; (d) Cao K, Wang Z and Zhao X, *Shiyong Daxue Xuebao Ziran Kexueban*, 2004, **28**, 100; (e) Ghosh S, Misra A K, Bhatia G, Khan M M and Khanna A K, *Bioorg Med Chem Lett.*, 2009, **19**, 386; (f) Tenchiu (Deleanu) A-C, Kostas I D, Kovala-Demertzi D and Aris Terzis, *Carbohydr Res.*, 2009, **344**, 1352.
- Nguyen Dinh Thanh and Nguyen Thi Thanh Mai, *Carbohydr Res.*, 2009, **344**, 2399.
- Loupy A, *Microwave in Organic Synthesis* (2nd Edition, Weinheim: Wiley-VCH Verlag GmbH & Co KGaA), 2006, **1**, 579-594.

21. (a) Lemieux R L, *Methods in Carbohydrate Chemistry*, Whistler R L, Wolfrom M L Eds. (New York: Academic Press), 1963, **2**, 221–222; (b) Bama K G and RaJani K B, *Indian J Chem.*, 1988, **27B**, 1157.
22. Ghosh S, Misra A K, Bhatia G, Khan M M and Khanna A K, *Bioorg Med Chem Lett.*, 2009, **19**, 386.
23. Martínez J, Adrio L A, Antelo J M, Ortigueira J M, Pereira M T, Fernández J J, Fernández A and Vila J M, *J Organomet Chem.*, 2006, **691** 2721.